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TITLE: Aortic Hemostasis and Resuscitation Advanced REBOA for NCTH and Reversal of HiTCA

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14. ABSTRACT The majority of combat and civilian casualties are due to severe uncontrolled, non-compressible hemorrhage resulting in cardiovascular collapse. Current resuscitation techniques, including cardiopulmonary resuscitation (CPR), thoracotomy, and aortic cross-clamping to reverse hemorrhage-induced traumatic cardiac arrest (HiTCA), are very invasive and ineffective for austere combat casualties. Aortic Hemostasis and Resuscitation (AHR) is advanced form of resuscitative endovascular balloon occlusion of the aorta (REBOA) that has been recently shown to promote return of spontaneous circulation (ROSC). This study examines the survival benefit of AHR in otherwise fatal non-compressible torso hemorrhage (NCTH) with HiTCA. It aims to compare the efficacy of the selective aortic arch perfusion (SAAP) catheter when used with fresh whole blood or an oxygen therapeutic (HBOC). In addition, it aims to demonstrate the feasibility of the conversion from SAAP therapy to limited extracorporeal life support (ECLS), and also to determine the impact of ECLS on critical physiology. To do this, we utilized a model of swine NCTH and HiTCA in a series of experiments in which each animal underwent a liver laceration and allowed to free bleed for five minutes through the SAAP catheter to achieve HiTCA. Then, resuscitation fluid is selectively perfused through the balloon catheter to the heart and brain, while also limiting non-compressible bleeding below the balloon. As a result, ROSC was achieved in 100% of the FWB animals and 86% of the HBOC-201 animals (p=0.12). Overall survival (t = 320 min) was 92% in the FWB group and 67% in the HBOC-201 group (p=0.12). This study shows that the SAAP catheter is an effective method of hemorrhage control by promoting ROSC and sustaining life in pre-hospital transport. AHR promotes hemodynamic stability and has the potential to fill a critical unmet gap in military and civilian trauma care.					
15. SUBJECT TERMS Non-compressible torso hemorrhage (NCTH), hemorrhage-induced traumatic cardiac arrest (HiTCA), resuscitative endovascular balloon occlusion of the aorta (REBOA), aortic hemostasis and resuscitation (AHR), hemoglobin-based oxygen carrier (HBOC), selective aortic arch perfusion (SAAP), extracorporeal life support (ECLS), extracorporeal membrane oxygenation (ECMO)					
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1. INTRODUCTION:

Uncontrolled, non-compressible hemorrhage resulting in cardiovascular collapse accounts for the majority of civilian and military casualties. Current techniques used against hemorrhage-induced cardiac arrest in severe combat casualty care have been shown to be ineffective, thus survival rates are low. In contrast, aortic hemostasis and resuscitation (AHR) has been shown to be effective in hemorrhage control. AHR with oxygenated whole blood and packed red blood cells has been shown to stimulate the return of spontaneous circulation (ROSC). SAAP is a technique in which a balloon catheter is introduced into the aorta and inflated to stop bleeding. This study aims to evaluate the effectiveness of selective aortic arch perfusion (SAAP) when used in combination with an external pump system that infuses either fresh whole blood or hemoglobin-based oxygen carrier (HBOC) to provide the body with oxygen after circulation is restored. The main objective is to demonstrate the survival benefit of AHR using a large animal model by effectively achieving ROSC, providing hemodynamic support, and increase pre-hospital transport and long-term survival.

2. KEYWORDS:

Non-compressible torso hemorrhage (NCTH), hemorrhage-induced traumatic cardiac arrest (HiTCA), resuscitative endovascular balloon occlusion of the aorta (REBOA), aortic hemostasis and resuscitation (AHR), hemoglobin-based oxygen carrier (HBOC), selective aortic arch perfusion (SAAP), extracorporeal life support (ECLS)

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?

Major Task 1/Phase I (Y1)

Subtask 1: Submit documents for IACUC approval

Milestone # 1 IACUC approval obtained (3/16/2016)

Subtask 2: Submit documents for ACURO approval

Milestone # 2 ACURO approval obtained (10/24/2016)

Subtask 3: Staff Hiring (Q2)

Subtask 4: Surgical capability Start-up including 6 pilot/model refinement animals

Subtask 5: Phase I study execution (two experimental groups): animal experiments – fresh whole

SAAP vs HBOC SAAP with critical care observation and limited ECLS as per protocol 24 with schedule for up to 4 technical failures experimental swine total (2 pig per 1-2 weeks); 60 donor swine (Completed 5/5/2017)

Subtask 6: QA of data entry, statistical analysis, and final study report (In Progress)

Major Task 2/Phase II (Y2)

Subtask 1: Development of didactic training component and recruit first class of five participants.

Subtask 2: Complete first AHR course. Assess and refine coursework. 16 swine for training; 30 donor swine.

Subtask 3: Recruit second class of five participants and complete second AHR course.

Subtask 4: QA of data entry, statistical analysis, and final study report.

What was accomplished under these goals?

1) Phase I experiments and data analysis have been completed in preparation of Y2/Phase II of training development.

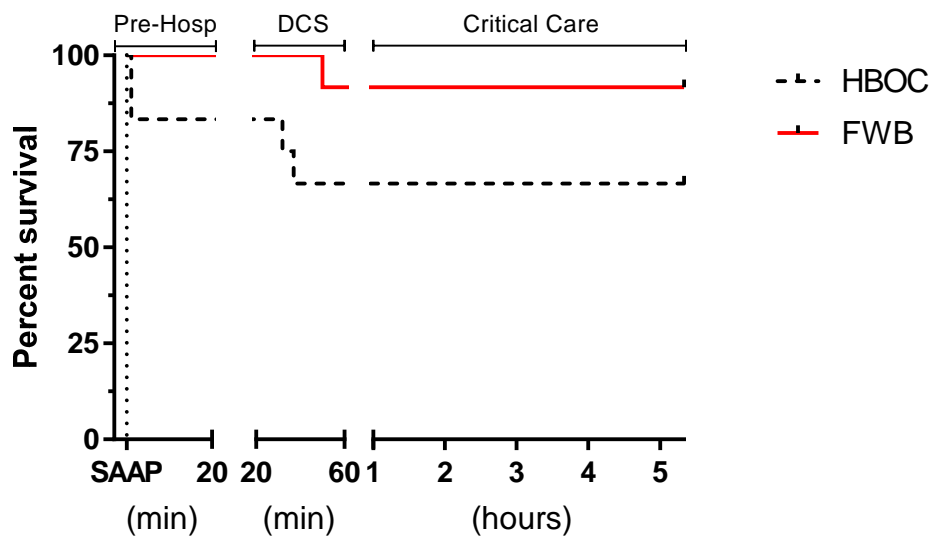
2) The objectives were to compare the efficacy of SAAP therapy between oxygenated HBOC and oxygenated FWB, and also to determine if SAAP can be converted to SAAP-ECMO therapy without negatively impacting critical physiology achieved by the aortic balloon occlusion.

In this study, the SAAP catheter is introduced into the aorta and inflated to stop bleeding while allowing the administration of oxygenated resuscitation from an external pump system directly into the heart during cardiac arrest to achieve ROSC.

3) The results show that HBOC-201 and fresh whole blood are both effective at promoting ROSC in HiTCA and that the conversion from SAAP to ECMO via the SAAP catheter is feasible.

All FWB animals achieved ROSC, while 12 of the 14 HBOC animals achieved ROSC. Five animals (4 HBOC, 1 FWB) died before the end of experiment. All animals except one that achieved ROSC survived pre-hospital and converted to ECLS.

All of the stated goals in Phase 1 were met. Full details of experimental outcomes and being prepared for publication. Analysis is ongoing.



What opportunities for training and professional development has the project provided?

Level II/III emergency care providers will be trained in the AHR technique in Y2 to demonstrate its military applicability and survival benefit prior to clinical use.

How were the results disseminated to communities of interest?

A Grand Rounds presentation was made at Baylor Dallas Medical Center, a facility that already employs trauma-ECMO technology and will provide training volunteers for the second phase of the project. In addition, AFMSA-SG5M has been briefed of the status of the current project as this project is part of a larger program of research joint funded in previous FYs by the USAF. Final analysis and outcomes will be distributed to relevant medical and line commands where technology may be implemented following successful clinical trials.

What do you plan to do during the next reporting period to accomplish the goals?

Develop the didactic training component, recruit participants, and train the emergency providers in the technique to demonstrate its feasibility. The training will be a combination of didactic lectures, vascular access training, and labs, using a non-recovered swine model of NCTH and HiTCA.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

The aim is for the results to demonstrate that AHR improves ROSC and survival of patients in pre-hospital transport, and ultimately in long-term survival. This likely could change the standard of hemorrhage control and resuscitation strategies.

In addition, HBOC has a longer shelf-life than fresh whole blood and may be a future alternative for human erythrocytes. It can be kept at room temperature for up to three years, does not have to be matched with blood type, and can be used on patients with immune systems that attack red blood cells. HBOC could potentially eliminate the need for whole blood in the use of SAAP technology, extending its pre-hospital viability in combat theaters of operation.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Primary impact is the potential adoption of a new resuscitation technique in military and civilian care. Results, use and training algorithms, and new practices will be transferred to both civilian and military centers through training programs and involvement of both civilian and military medical centers in upcoming clinical trials.

What was the impact on society beyond science and technology?

SAAP and AHR have been shown to increase the likelihood of achieving ROSC, thus survival rates of patients will likely increase, which will decrease the number of fatalities after non-compressible torso hemorrhage (NCTH) and hemorrhage induced traumatic cardiac arrest (HiTCA).

- 5. CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, “Nothing to Report,” if applicable:

Changes in approach and reasons for change

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them

Variable RPM design of Cardiohelp pump and high pressure feedback from SAAP catheter made calcium infusion matching with fresh whole blood challenging. A two-pump system solution was implemented to facilitate pre-hospital use of SAAP before converting to partial ECLS. Discussion ongoing with Maquet (Cardiohelp manufacturer) to accommodate advanced devices like the SAAP catheter. Close monitoring and maintenance of tight control of the calcium/fresh whole blood ratio during experiments helps to minimize ventricular fibrillation during HiTCA.

Changes that had a significant impact on expenditures

Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

No human subject research performed in the completion of Y1/Phase I. A human use protocol **may** be required for the education and training portion of the Y2/Phase II studies.

Significant changes in use or care of vertebrate animals.

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**
Report only the major publication(s) resulting from the work under this award.

Journal publications.

American Heart Association Resuscitation Conference Abstract submission June 12, 2017. Draft manuscript of results being prepared for submission to Circulation.

Books or other non-periodical, one-time publications.

Nothing to Report

Other publications, conference papers, and presentations.

Presented at Baylor University Medical Center's Grand Rounds in Dallas May 11, 2017

- **Website(s) or other Internet site(s)**

Nothing to Report

The primary product is the AHR/SAAP catheter technique which uses an oxygenated fluid to achieve ROSC in order to sustain post-ROSC survival until vascular control of hemorrhage occurs to promote overall long-term survival. SAAP technology is owned by the University of North Carolina and by Resuscitech INC. Resuscitech INC is in the process of manufacturing and pre-FDA submission for SAAP catheters. Use of the SAAP technique in HiTCA will be shared via the training program developed in the second year of this project in addition to worldwide speaking engagements and clinical trials.

- **Inventions, patent applications, and/or licenses**

Nothing to Report

- **Other Products**

The primary reportable outcome of the first phase of this project is an enhanced understanding of the following: 1) use of non-blood product substrates with SAAP perfusion and 2) technical feasibility of transition from SAAP to SAAP-ECLS for cardiac support during critical care.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	James D Ross, PhD
Project Role:	PI
Research Identifier:	NA
Nearest Person Month Worked:	3
Contribution to Project:	ACURO documentation preparation and submission. Pilot experiment execution. Pilot data evaluation. Report preparation. Control administration of blood products. Monitor animals during experiments. Full study execution including surgical procedures, ECMO circuit/pump management and critical care decision making.
Name:	James Manning, MD
Project Role:	
Research Identifier:	NA
Nearest Person Month Worked:	4
Contribution to Project:	Developer of SAAP catheter. Monitor animals during experiment. Critical care decision making. Analysis of data and outcomes.
Name:	Todd Graham
Project Role:	Research Technician
Research Identifier:	NA
Nearest Person Month Worked:	9
Contribution to Project:	Laboratory equipment set-up and maintenance. Coordination of equipment training protocols. Development of BIOPAC data acquisition templates. Development of consumable supply ordering schedules for phase I. Execution of laboratory experiments. Coordination of data review.
Name:	Brianne Madtson
Project Role:	Research Technician
Research Identifier:	NA
Nearest Person Month Worked:	9
Contribution to Project:	Laboratory equipment maintenance. Pump technology testing and calibration. Production of run-sheets and laboratory/OR scheduling and turnover for final experiments. Loading blood products for administration.
Name:	Rondi Dean
Project Role:	Research Technician
Research Identifier:	NA
Nearest Person Month Worked:	3
Contribution to Project:	Animal schedule coordination. Consumable supply ordering. Laboratory set-up and equipment maintenance. DEA licensure coordination and schedule drug ordering. Capital equipment requisition for phase I.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

What other organizations were involved as partners?

The project included a subaward collaboration with the Co-PI, Dr. James Manning, and his laboratory at University of North Carolina as detailed in the contract subaward. All experiments were performed on-site at Oregon Health and Science University.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A

QUAD CHARTS: N/A

9. APPENDICES: N/A